Institute Report No. 304

Primary Dermal Irritation Potential of Diethyleneglycol Dinitrate (DEGDN) in Rabbits

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and
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MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

October 1988

Toxicology Series: 154

LETTERMAN ARMY INSTITUTE OF RESEARCH
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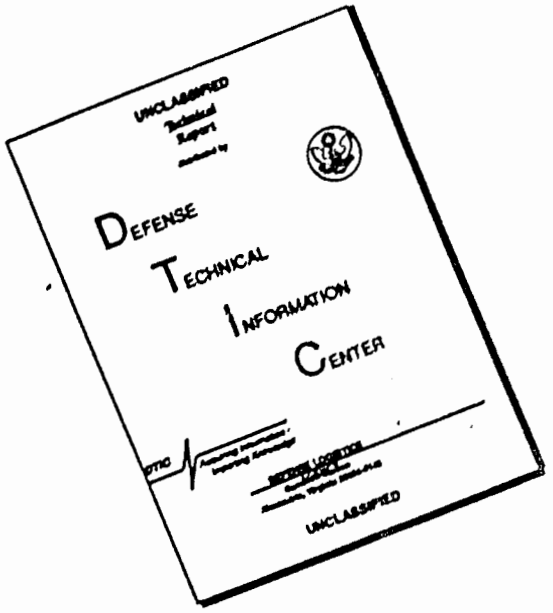

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Edwin S. Beatrice 26 Oct 88

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COL, MC
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The primary dermal irritation potential of diethyleneglycol dinitrate (DEGDN) was determined in New Zealand White rabbits using a modified Draize procedure. The test compound was classified as a nonirritant following a 4-hour application period. Neither edema, erythema, nor any other recognizable skin reaction was detected at any time during the 72-hour observation period.

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ABSTRACT

The primary dermal irritation potential of diethyleneglycol dinitrate (DEGDN) was determined in New Zealand White rabbits using a modified Draize procedure. The test compound was classified as a nonirritant following a 4-hour application period. Neither edema, erythema, nor any other recognizable skin reaction was detected at any time during the 72-hour observation period.

Key Words: Primary Dermal Irritation, Diethyleneglycol Dinitrate, DEGDN, Rabbit, Munitions

PREFACE

TYPE REPORT: Primary Dermal Irritation GLP Study Report

TESTING FACILITY:

US Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR:

US Army Medical Research and Development Command
US Army Biomedical Research and Development Laboratory
Fort Detrick, Maryland 21701-5010
Project Officer: Gunda Reddy, PhD

PROJECT/WORK UNIT/APC: 3E162720A835/180/TLB0

GLP STUDY NUMBER: 85004

STUDY DIRECTOR: MAJ Don W. Korte, Jr, PhD, MSC

PRINCIPAL INVESTIGATOR: MAJ Larry D. Brown, DVM, VC,
Diplomate, American College of
Veterinary Preventive Medicine

PATHOLOGIST: MAJ John C. Turnier, DVM, VC, USAR
Diplomate, American College of
Veterinary Pathologists

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Diethyleneglycol Dinitrate (DEGDN)

INCLUSIVE STUDY DATES: 25 Jul - 3 Sep 85

OBJECTIVE: The objective of this study was to determine the primary dermal irritation potential of diethyleneglycol dinitrate (DEGDN) in New Zealand White rabbits.

ACKNOWLEDGMENTS

The authors wish to thank the following individuals for their contribution to the successful completion of this study: Gerald F.S. Hiatt, PhD, SSG James D. Justus, BS, and SP4 John R.G. Ryabik, BS, for their assistance with this research; Richard A. Spieler, SP4 Scott L. Schweb[illegible], SP4 James J. Fischer, SP4 Theresa L. Polk, Obie Goodrich, Diane Arevalo, CPT Thomas Pool, DVM, and PVT Greg Rothammer for animal care; and Colleen S. Kamiyama, Dorothy Davis, and Dianna Johnson for secretarial assistance. Eleanor M. Baker proofread the manuscript.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY:

We, the undersigned, declare that GLP Study 85004 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte, Jr 11 OCT 88

DON W. KORTE,JR., PhD / DATE
MAJ, MSC
Study Director

Larry D. Brown

LARRY D. BROWN, DVM / DATE
MAJ, VC
Principal Investigator

Conrad Wheeler 11 OCT 88

CONRAD R. WHEELER, PhD / DATE
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Analytical Chemist

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ATTENTION OF:

SGRD-ULZ-QA 13 October 1988

MEMORANDUM FOR RECORD

SUBJECT: GLP Statement of Compliance

1. This is to certify that the protocol for GLP Study 85Ø04 was reviewed on 5 March 1985.

2. The institute report entitled "Primary Dermal Irritation Potential of Diethylene Glycol Dinitrate (DEGDN) in Rabbits," Toxicology Series 154, was audited on 1Ø August 1987.

Carolyn M. Lewis

CAROLYN M. LEWIS
Chief, Quality Assurance

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

Primary Dermal Irritation Potential of Diethyleneglycol Dinitrate (DEGDN) in Rabbits--Brown and Korte

INTRODUCTION

The Department of Defense is considering the use of either diethyleneglycol dinitrate (DEGDN), triethyleneglycol dinitrate (TEGDN), or trimethylolethane trinitrate (TMETN) as a replacement for nitroglycerin in new propellant formulations. However, considerable gaps in the toxicology data of the compounds were identified during a review of their health effects (1) conducted for the US Army Biomedical Research and Development Laboratory (USABRDL). Consequently, USABRDL has tasked the Division of Toxicology, Letterman Army Institute of Research (LAIR), to conduct an initial health effects evaluation of the proposed replacement nitrate esters. This initial evaluation of DEGDN, TMETN, TEGDN, and two DEGDN-based propellants, JA-2 and DIGL-RP, includes the Ames mutagenicity assay, acute oral toxicity tests in rats and mice, acute dermal toxicity in rabbits, dermal and ocular irritation studies in rabbits, and dermal sensitization studies in guinea pigs.

Objective of Study

The objective of this study was to determine the primary dermal irritation potential of diethyleneglycol dinitrate (DEGDN) in New Zealand White rabbits.

MATERIALS

Test Substance

Chemical Name: Diethylene Glycol Dinitrate (DEGDN)

Chemical Abstracts Service Registry No.: 693-21-0

LAIR Code No.: TM64

Molecular structure:

$$O_2N\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}NO_2$$

Molecular Formula: $C_4H_8N_2O_7$

Other test substance information is presented in Appendix A.

Vehicle

Diethylene glycol dinitrate (DEGDN) is a liquid at room temperature; therefore, a vehicle was not required.

Animal Data

Six male and two female New Zealand White rabbits (Elkhorn Rabbitry, Watsonville, CA; USDA No. 93A7A), identified individually with ear tattoos numbered 85F121, 85F141 to 85F144 inclusive, and 85F146 (males) and 85F129 and 85F131 (females), were assigned to the study. Animal 85F129 (female) was submitted for quality control necropsy on 12 Jul 85, and rabbit 85F143 (male) was sacrificed on 13 Aug 85 due to traumatic ulcerative pododermatitis. The remaining six animals (five males and one female) were dosed. The animal weights on dosing day (20 Aug 85) ranged from 3.0 to 3.6 kilograms. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, battery-type cages with screened floors and automatically flushing dumptanks. The diet consisted of 150 g/day of Certified Purina Chow® Diet 5322 (Ralston Purina Company, St Louis, MO); water was provided by continuous drip from a central line. The animal room temperature was maintained at 15.5 to 25°C with a relative humidity range of 42 to 60% with occasional spikes to 65% during room cleaning. The photoperiod was 12 hours of light per day.

METHODS

Acclimation and Group Assignment

Study animals were initially assigned to GLP study 85029 for 25 days following a 14-day quarantine by the Division of Animal Care and Services. They were treated once

prophylactically for ear mites with Canex® and mineral oil while under quarantine. During this period they were observed daily for signs of illness; they were not dosed. On 19 Aug 85, the animals were transferred to GLP study 85004, clipped, and quadrants marked. On 20 Aug 85, the animals were dosed.

Dosage Levels

A standard dose of 0.5 ml DEGDN was used for the test compound sites.

Compound Preparation

The test compound was received as a solution containing 18% acetone. The acetone was removed by evaporation before studies with the propellant (Appendix A).

Chemical Analysis of Dosing Solution

DEGDN was analyzed for purity and stability (Appendix A). The reformulated DEGDN was sufficiently pure and stable for use in the test procedures.

Test Procedures

This study was conducted in accordance with EPA guidelines (2) and LAIR SOP-OP-STX-34 (3).

The backs of six rabbits were close-clipped 24 hours before dosing and divided into four unabraded quadrants designated I-IV (1,5). Each animal had two sites (II, III) treated with the test compound. Site I was a sham control (no treatment) site and site IV a sham gauze patch control. A dose of 0.5 ml of DEGDN was placed on a 1-inch square gauze patch which was taped to the appropriate site. Blenderm® (Medical Products Division of 3M, St Paul, MN), a semi-impervious hypoallergenic surgical tape, was used to hold the patches in place. Vetrap® (Animal Care Products Division of 3M, St. Paul, MN) was then wrapped securely around the animal. The test compound was left in contact with the skin for 4 hours. At the end of the exposure period, the wrapping and patches were removed and the skin was gently wiped if the test material had adhered to it, and the areas were scored one hour later.

Observations

The grading and scoring for dermal reactions were performed according to Table 1 (4). Scoring and grading of

TABLE 1

Evaluation of Skin Reactions

Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness to slight eschar formation, injurious in depth)	4
Possible total erythema score	**4***
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (edges raised approx. 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Possible total edema score	**4***
Possible total score for primary irritation	**8**

*Any skin reaction more serious than severe edema, vesiculation, ulceration, or necrosis places the chemical in Category V.

dermal reaction were performed at 1, 24, 48, and 72 hours after removal of the patches. Routine observations for clinical signs were made daily from 20 Aug to 3 Sep 85.

Duration of Study

Appendix C is a complete listing of historical events.

Changes/Deviations from Original Protocol

This study was conducted in accordance with applicable SOPs, the protocol, and addenda, excepting the sex of the animals included both males (6) and females (2) rather than all females. This deviation did not affect the outcome of this study.

Storage of the Raw Data and Final Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTS

Results from scoring the dermal irritation in each rabbit are tabulated in Appendix D. All scores were negative. Neither edema, erythema, nor any other recognizable skin reaction was detected at any time during the 72-hour observation period.

The six dosed animals were submitted for gross necropsy on 3 Sep 85. There were no signs of skin irritation in any of the animals. The Veterinary Pathologist's Report is presented as Appendix E.

DISCUSSION

The modified Draize dermal irritation test as performed for this study has proven reliable for detecting non-irritating substances and severe irritants but considerably less reliable for detecting mild and moderate irritants (5). Consequently, many systems have been used to score and categorize the dermal irritation potentials of a test compound. The system used by the Division of Toxicology, LAIR, is an adaptation of one used at the US Army Environmental Hygiene Agency (6). It develops a dermal irritation index based on the peak net mean score, which is the maximum net mean score calculated during the 72-hour

observation period. Test compounds are classified as nonirritants or irritants based on the following scale:

Classification	Peak Net Mean Score
Nonirritant	0.0 - 0.5
Mild Irritant	0.6 - 2.0
Moderate Irritant	2.1 - 5.0
Severe Irritant	5.1 - 8.0

Topically applied DEGDN produced neither edema nor erythema at any test site on six rabbits. Also, all sham sites were negative for dermal reactions. Therefore, the Peak Net Mean Score for DEGDN was zero. Based on these findings, DEGDN was classified as a nonirritant.

CONCLUSION

Diethyleneglycol dinitrate (DEGDN) should be classified as a nonirritant since it causes no grossly detectable dermal reactions under conditions of this study.

REFERENCES

1. Holleman JW, Ross RH, Carroll JW. Problem definition study on the health effects of diethyleneglycol dinitrate, triethyleneglycol dinitrate, and trimethylolethane trinitrate and their respective combustion products. Frederick, MD: US Army Medical Bioengineering Research and Development Laboratory, 1983, DTIC No. ADA 127846.

2. Environmental Protection Agency. Office of Pesticides and Toxic Substances, Office of Toxic Substances (TS-792). Primary dermal irritation. In: Health effects test guidelines. Washington, DC: Environmental Protection Agency, August 1982; EPA 560/6-82-001.

3. Primary dermal irritation study. LAIR Standard Operating Procedure OP-STX-34. Presidio of San Francisco, CA: Letterman Army Institute of Research, 19 March 1982.

4. Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 83:377-390.

5. McCreesh AH, Steinberg M. Skin irritation testing in animals. In: Marzulli FN, Maibach HI, eds. Dermatotoxicology. 3rd ed. Washington, DC: Hemisphere Publishing Corp., 1987: 153-172.

6. US Army Environmental Hygiene Agency (AEHA). Topical hazard evaluation program. Procedural guide. Aberdeen Proving Ground, MD: US Army Environmental Hygiene Agency, October, 1985.

Appendix A: CHEMICAL DATA

Chemical name: Ethanol, 2,2'-oxybisdinitrate

Alternate chemical name: Diethyleneglycol dinitrate (DEGDN)

Chemical Abstracts Service Registry No.: 693-21-0

LAIR Code No.: TP047

Chemical structure:

$$O_2N\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}NO_2$$

Molecular formula: $C_4H_8N_2O_7$

Molecular weight: 196

Physical state: Pale yellow liquid

Density (g/cm^3): 1.38[1]

Analytical data: Refer to the attached data sheet, ARRCOM Form 213R. The compound chromatographed as a single peak (retention time 5.4 min) by HPLC analysis under the following conditions: column, Brownlee RP-18 (4.6 x 250 mm); solvent system, 30% water, 70% acetonitrile; flow rate, 0.9 ml/min; detection wavelength, 205 nm.[2] NMR (300 MHz, CD_3CN): 3.75 δ (complex multiplet, 4H, $-CH_2-O-CH_2-$), 4.61 complex

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[1] Holleman JW, Ross RH, Carroll JW. Problem definition study on the health effects of diethyleneglycol dinitrate, triethyleneglycol dinitrate, and trimethylolethane trinitrate and their respective combustion products. Frederick, MD: US Army Medical Bioengineering Research and Development Laboratory, 1983; DTIC No. ADA127846, p. 17.

[2] Wheeler CR. Toxicity Testing of Propellants. Laboratory Notebook #85-12-023, p. 31. Presidio of San Francisco, CA: Letterman Army Institute of Research.

Appendix A (cont.): CHEMICAL DATA

multiplet, 4H,-CH_2ONO_2).[3] Additional singlet signals of approximately equal intensity were observed at 2.08 d, and were due to sample impurities. Integration of all signals in the spectrum demonstrated that the sample contained 96.6% DEGDN. The impurities were not identified. IR(KBr): 2896, 1632, 1429, 1390, 1373,1279, 1139, 1032, 909, 857, 758, 707, 655, 572cm^{-1}.[4]

Stability: The DEGDN was shipped containing 18% acetone (a desensitizer) and arrived at LAIR on 12 December 1984. The acetone was removed by rotary evaporation prior to studies with the propellant. Analysis of the compound one year after it was received gave the results described above. Stability of the compound in corn oil (the dosing vehicle) was examined. As determined by HPLC, the concentration of DEGDN in corn oil emulsions 24 h after preparation was within 1% of the target value.[5]

Source: Radford Army Ammunition Plant, Radford, Virginia (prime contractor: Hercules Inc., Wilmington, Delaware).

Lot No.: RAD84M001S214

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[3] Ibid. pp. 44-48.

[4] Ibid. pp. 49-50.

[5] Wheeler CR. Nitrocellulose - Nitroguanidine Projects. Laboratory Notebook #85-01-006, pp. 57-60. Presidio of San Francisco, CA: Letterman Army Institute of Research.

Appendix A (cont): CHEMICAL DATA

DESCRIPTION SHEET FOR EXPLOSIVES, CHEMICALS, ETC

REPORTS CONTROL SYMBOL: EXEMPT-Para 7-2a AR 335-15 | PAGE 1 OF 1 pg

TO:

FROM:

DATE: December 5, 1984

MATERIAL: Diethylene Glycol Dinitrate (DEGDN)

MANUFACTURER: HERCULES INCORPORATED
RADFORD ARMY AMMUNITION PLANT

CONTRACT NO.: DAAA09-77-C-4007

SECTION A - DESCRIPTION OF LOTS

FROM NUMBER	THRU NUMBER	TOTAL NO. LOTS	TOTAL NET AMOUNT ACCEPTED
RAD84M001S214	-	1	5 lbs

PLACE MANUFACTURED: RADFORD ARMY AMMUNITION PLANT, RADFORD, VIRGINIA

SPECIFICATION AND AMENDMENT/DRAWING NO.: DOD-D-64015

SECTION B - DESCRIPTION OF MATERIAL

Requirements	Limit	Results
82.2°C Potassium Iodide Starch Paper Heat Test (KI)	10 minutes minimum	12
Nitrogen, %	14.10 minimum	14.15
Water, %	Info Only	0.43
Acidity	None	None
Alkalinity	None	None

REMARKS: DEGDN is desensitized with 15% or more of acetone for a total weight of 5 lbs. and packed in a DOT 6D 5 gallon drum with a DOT 2S liner, overpacked in a DOT-6J 30 gallon capacity drum with vermiculite as a cushioning agent around the 5 gallon drum and contained in the 30 gallon drum. Requested by shipping Order AMCCOM and COR letter SMCRA dated November 28, 1984 (DOT Exemption 5704).

SECTION C - CERTIFICATION

SAMPLING CONDUCTED BY: HERCULES INCORPORATED

TESTING CONDUCTED BY: HERCULES INCORPORATED

THE ABOVE MATERIAL COMPLIES WITH ALL SPECIFICATION REQUIREMENTS AND IS CERTIFIED TRUE AND CORRECT.

12-5-84 (DATE) — [signature] (SIGNATURE) P.A. WALKER

THE ABOVE DESCRIBED LOTS ARE HEREBY ACCEPTED

Dec 6, 1984 (DATE) — (TITLE) — FOR THE COMMANDER [signature] (SIGNATURE)

ARRCOM Form 213-R, 10 Aug 77 SEQUENCE No. 374

Appendix B: ANIMAL DATA

Species: *Oryctolagus cuniculus*

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA 95076

Sex: Male and Female

Age: Young Adults

Animals in each group: 6 males and 2 females

Condition of animals at start of study: Normal

Body weight range at dosing: 3.0 - 3.6 kg

Identification procedures: Ear tattoo procedure (SOP OP-ARG-1), tattoo numbers 85F121 and 85F141-144 inclusive and 85F146 (males) and 85F129 and 85F131 (females).

Pretest conditioning:

1. Quarantine from 11 Jul - 25 Jul 1985

2. Animals were close-clipped and examined 24 hours before dosing.

Justification: Laboratory rabbits are a proven sensitive animal model for dermal testing.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
11 Jul 85	Animals arrived at LAIR. They were examined for illness and placed under a two-week quarantine by the Division of Animal Care and Resources Group (ACS).
15 Jul 85	Animals' ears were tattooed.
19 Jul 85	Animals' ears were treated with Canex® and mineral oil for prevention of ear mites.
12-25 Jul 85	Animals were checked daily by ACS personnel.
22 Jul 85	Animal 85F129 was submitted for quality control necropsy.
25 Jul 85	Rabbits were removed from quarantine and assigned to GLP Study 85029 after being certified healthy by ACS Staff Veterinarian.
12,19,25 Jul; 8,20,27 Aug; 3 Sep 85	Animals were weighed.
25 Jul-3 Sep 85	Animals were checked daily by Toxicology Suite personnel.
13 Aug 85	Animal 85F143 was sacrificed due to ulcerative pododermatitis.
19 Aug 85	Six animals were close clipped and quadrant areas marked.
20 Aug 85	Test substance was applied and animals were wrapped. Bandages were removed 24 hours after exposure.
20 Aug 85	Animals were scored 1 hour after exposure.
21 Aug 85	Animals were scored 24 hours after exposure.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
22 Aug 85	Animals were scored 48 hours after exposure.
23 Aug 85	Animals were scored 72 hours after exposure.
3 Sep 85	Animals were submitted to Pathology Branch for sacrifice and necropsy.

APPENDIX D: Primary Irritation Data

Animal No.	30-60 min			24 h			48 h			72 h		
	Test	Sham	Vehicle	Test	Sham	Vehicle	Test	Sham	Vehicle	Test	Sham	Vehicle
85F121	0	0	0	0	0	0	0	0	0	0	0	0
85F131	0	0	0	0	0	0	0	0	0	0	0	0
85F141	0	0	0	0	0	0	0	0	0	0	0	0
[illegible]142	0	0	0	0	0	0	0	0	0	0	0	0
85F144	0	0	0	0	0	0	0	0	0	0	0	0
85F146	0	0	0	0	0	0	0	0	0	0	0	0
Peak Mean	0	0	0	0	0	0	0	0	0	0	0	0
Net Mean*	0			0			0			0		

*Net Mean equals Test Mean minus the greater of the Sham or Vehicle Mean. The peak or highest Net Mean for all observation periods is used to classify the test compound. A zero peak net mean score places DEGDN in Primary Skin Irritation Category I.

APPENDIX E: Pathology Report

LAIR Gross Pathology Report
GLP Study 85004

Test: Primary Dermal Irritation.

Investigator: MAJ Larry Brown.

Species: Rabbit (NZW).

Test Substance: DEGDN (Cas No. 693-21-0).

History: This study was conducted IAW SOP-OP-STX-34, and involved application of the compound to shaved sites of skin for predetermined periods of time and dosages.

Gross findings:

ANIMAL ID#	LAIR ACC#	FINDINGS
85F121	38216	Cecum - Pinworms in lumen
85F131	38217	Cecum - Pinworms in lumen
85F141	38218	Cecum - Pinworms in lumen Lungs - Red mottling Trachea - Red foamy contents
85F142	38219	Cecum - Pinworms in lumen
85F144	38220	No lesions recognized
85F146	38221	Cecum - Pinworms in lumen

Comment: The findings in animal #85F141 were not considered to be related to the administration of test substance. There were no signs of skin irritation in any of the animals.

JOHN C. TURNIER, DVM
MAJ, VC
Comparative Pathology Branch

17 March 1986

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